

c4 29. (Amended) A pharmaceutical composition selected according to the method of claim 1, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

Please add claim 38 as follows:

c5 38. (New) A method of treating an immune-mediated disorder comprising administering to a patient in need of such treatment a pharmaceutical composition according to claim 29.

### REMARKS

Claims 1-37 are pending in the instant application. Claims 1-6 and 29 have been amended and claim 38 has been added. Accordingly, following entry of the present amendment, claims 1-38 will be pending.

As amended, the pending claims are directed to a method for selecting a treatment for an immune-mediated disorder as well as methods of treatment and pharmaceutical compositions selected according to the method. Support for the amended claims can be found throughout the specification and the claims as originally filed. For example, as described at page 3, lines 16-18; at page 3, lines 21-23; at page 3, lines 29-31; at page 4, lines 1-3; at page 4, lines 7-9; at page 4, lines 14-25; at page 4, line 32 to page 5, line 5; at page 5, lines 21-32; and in Examples 1-4 of the specification, the present invention provides, for the first time, methods for selecting particular combinations of corticosteroids and gold compounds which are tailored to treat a particular immune disease in a more effective and safe manner.

More particularly, as stated, for example, at page 3, lines 16-18, of the specification, the invention provides methods "wherein at least one corticosteroid is selected to interact synergistically with a gold compound to exhibit preferential action towards one of the manifestations of [an immune] disorder or to exhibit equal action towards each manifestation of said disorder." In addition, Examples 2-4 (pages 12-24) illustrate how to select such treatments using mouse models in which the presence of one or more components of an immune disorder (*i.e.*, an inflammatory component and/or a cellular hyperproliferative component) has been

identified. These Examples illustrate how to select combinations of corticosteroids and gold compounds which are tailored to treat only one component of the disorder if only one exists, or both components if both exist and, thus, provide a more effective and safer treatment.

Specifically, the presence of either epidermal hyperplasia, dermal inflammatory cell infiltration, or both of these components, was identified in TPA treated mice, and the effects of various combinations of corticosteroids and gold compounds were tested for their efficacy in treating one or both of the components (see, *e.g.*, page 3, line 1; page 14, lines 8-10; page 22, lines 18-24; and page 23, lines 29-33).

As shown in the results presented in, *e.g.*, Tables 2-4, the present invention demonstrates for the first time the differential efficacy of various corticosteroids in inhibiting inflammation and/or hyperplasia. The present invention further demonstrates that different corticosteroids inhibit inflammatory and hyperplastic effects by different mechanisms (page 17, lines 15-16). The present invention further demonstrates that certain, but not all, corticosteroids have a synergistic effect in inhibiting inflammation and/or hyperplasia when combined with auranofin (see *e.g.*, Tables 9 and 10).

Attached hereto is a marked-up version of the changes made to the claims by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

No new matter has been added. Any amendments to and/or cancellations of the claims should be in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

**Rejection of Claims 1-5, 7-8, 11-15, 18, 21-22, 27 and 29-37 Under 35 U.S.C. § 102(b)**

The Examiner has maintained the rejection of claims 1-5, 7-8, 11-15, 18, 21, 22, 27 and 29-37 under 35 U.S.C. § 102(b) as being anticipated by Papandrea (AU-34351/89). Specifically, the Examiner is of the opinion that Papandrea teaches treatment of local or systemic inflammatory conditions using a composition comprising a gold compound and a corticosteroid and, thus, that the instant claims are anticipated by Papandrea.

Applicants respectfully traverse this rejection. As amended, the pending claims are directed to a method of selecting a treatment for an immune mediated disorder having an inflammatory component and/or a cellular hyperproliferation component by identifying the presence of one or both of the components; and then selecting at least one corticosteroid which interacts with a gold compound to exhibit preferential synergistic action towards the one component of the disorder if only one component is present, or to exhibit equal action towards each component of said disorder if both components are present. The pending claims are also drawn to pharmaceutical compositions selected according to this method.

By way of brief background, immune-mediated disorders are presented in several ways, each recognized as a specific form (i.e., "component") of the disorder. Such disorders can have an inflammatory component and/or a cellular hyperproliferative component. Both components can manifest at the same time or one component can be the predominant "lesion" or form of the disease. In such diseases where there is more than one arm or manifestation of the disorder, particularly if they are dissociated or apparently dissociated events (e.g., inflammatory and cellular hyperproliferation), it is desirable to be able to treat one or other of the manifestations of the disease only, thus avoiding the possible side effects of unnecessary treatment. On the other hand, if both manifestations of the disease are apparent and require treatment, appropriate selection of agents can be made.

The present invention is based on the unexpected finding that different corticosteroids synergise with gold compounds in a different way. With some, the synergy exhibited is toward the inflammatory components of the disease only, and with others it is toward the cellular hyperproliferation only. The synergy toward the other manifestation of the disease is non-existent. Accordingly, the present invention enables for the first time the selection of one or more corticosteroids to achieve a synergistic composition with improved efficacy and safety toward a particular component of a multi-component disease.

In contrast, Papandrea teaches treatment of psoriasis using a combination of auranofin and betamethazone dipropionate, without regard to the fact that different corticosteroids differ in the manner and degree in which they interact with auranofin to treat the disease. Indeed, the assumption in the art at the time of the present invention was that all corticosteroids behaved similarly. Thus, Papandrea fail to teach or suggest a process of selecting a particular treatment

for an immune disorder, as claimed by Applicants, namely one involving the identification of an inflammatory component and/or a cellular hyperproliferation component, followed by selection of at least one corticosteroid which interacts with a gold compound to exhibit preferential synergistic action towards one or both components of the disorder depending on whether one or both are present. Nor do Papandrea teach or suggest a composition selected according to this method.

Accordingly, for at least the foregoing reasons, the pending claims are novel over Papandrea and, thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-5, 7-8, 11-15, 18, 21, 22, 27 and 29-37 under 35 U.S.C. §102(b).

**Rejection of Claims 1-5, 7-8, 11-15, 18, 21-22, 27 and 29-37 Under 35 U.S.C. §102(e)**

The Examiner has maintained the rejection of claims 1-5, 7-8, 11-15, 18, 21-22, 27 and 29-37 under 35 U.S.C. §102(e) as being anticipated by Papandrea (US Pat. No. 5,527,779). Specifically, the Examiner maintains that "[t]he composition and method of use taught by the reference are encompassed by the instant claims."

Applicants respectfully traverse this rejection. For the same reasons provided above in response to the rejection over Papandrea (AU-34351/89) under 102(b), the pending claims as amended herein are novel over Papandrea (US 5,527,779) under 102(e). Neither Papandrea reference, AU-34351/89 or US 5,527,779, teaches a process of selecting a particular treatment for an immune disorder, as claimed by Applicants, namely one involving the identification of an inflammatory component and/or a cellular hyperproliferation component, followed by selection of at least one corticosteroid which interacts with a gold compound to exhibit preferential synergistic action towards one or both components of the disorder depending on whether one or both are present. Nor does either Papandrea reference teach or suggest a composition selected according to this method.

Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 1-5, 7-8, 11-15, 18, 21-22, 27 and 29-37 under 35 U.S.C. §102(e) as being anticipated by Papandrea (US Pat. No. 5,527,779).

**Rejection of Claims 1-37 Under 35 U.S.C. §103(a)**

The Examiner has maintained the rejection of claims 1-37 under 35 U.S.C. §103(a) as being unpatentable over Papandrea (AU-34351/89 or US 5,527,779). The Examiner is of the opinion that, based on the state of the prior art combined with the level of skill of one having ordinary skill in the pharmaceutical arts, "the combination of one or two corticosteroids with a gold compound for the treatment of an immune-mediated disorders, such as rheumatoid arthritis, dermatitis and psoriasis, would have been obvious to one having ordinary skill in the art at the time of the invention and the administration of the composition by the recited routes of administration is within the level of skill of the ordinary artisan and, thus, is prima facie obvious."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the one of ordinary skill in the art at the time it was made. At the time of the present invention, it was assumed that all corticosteroids behaved in the same manner to treat immune disorders. This is shown by the fact that Papandrea merely teach the use of auranofin and betamethazone dipropionate to treat psoriasis, without any teaching or suggestion whatsoever that other combinations of corticosteroids and gold compounds may act differently (e.g., better or worse, or in a different manner) to treat the disease. Accordingly, based on the prior art at the time of the present invention, it certainly would not have been obvious to have tried selecting particular combinations for a given immune disorder. Indeed, how could there have been motivation to have done so if it was not even known in the prior art that corticosteroids had such a differential synergistic effect in combination with gold compounds in treating such diseases?

In sum, the teachings of the prior art, including Papandrea, simply would not have provided sufficient motivation at the time of the invention to have practiced the presently claimed method of selecting a treatment for an immune disorder based on the differential synergistic interaction that exists between corticosteroids and gold compounds, let alone any guidance on how such selections could be made. Based on the fact that this differential synergy was not even recognized at the time of the invention, there would not have been any motivation for one of ordinary skill in the art to have gone about the steps of identifying whether one or both components (i.e., inflammation and cellular hyperproliferation) of the immune disease were

present; and then selecting a particular combination of one or more corticosteroids and gold compounds to exhibit preferential synergistic action toward the one or both components.

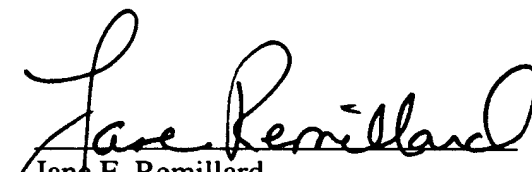
Accordingly, for at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-37 under 35 U.S.C. §103(a) as being unpatentable over the Papandrea publications.

**CONCLUSION**

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Specification:**

The caption beginning at page 21, line 12 was replaced with the following:

**--Example 4 2: Synergistic Effect of Auranofin and Corticosteroids With Different Clinical Potencies.--**

**In the claims:**

Claims 1-6 and 29 have been amended as follows:

1. (Amended) A method of selecting a treatment for treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising identifying the presence of one or both of said components; and selecting the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid which is selected to interact with the a gold compound to exhibit preferential synergistic action towards the one of the components of said disorder if only one component is present or to exhibit equal action towards each component of said disorder if both components are present, and provided that said method does not include the administration of a combination of auranofin and betamethazone dipropionate.

2. (Amended) A method of ~~treating an immune-mediated disorder~~ according to claim 1, wherein the disorder has an inflammatory component and a cellular hyperproliferation component.

3. (Amended) A method of ~~treating an immune-mediated disorder~~ according to claim 1, wherein the gold compound and the at least one corticosteroid are administered simultaneously.



4. (Amended) A method ~~of treating an immune-mediated disorder~~ according to claim 1, wherein the gold compound and the at least one corticosteroid are administered sequentially.

5. (Amended) A method ~~of treating an immune-mediated disorder~~ according to claim 4, wherein the at least one corticosteroid is administered after the gold compound.

6. (Amended) A method ~~of treating an immune-mediated disorder~~ according to claim 1, comprising selecting ~~the step of administering~~ at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

29. (Amended) A pharmaceutical composition selected according to the method of claim 1, ~~comprising a the gold compound and the at least one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an the inflammatory component and/or a the cellular hyperproliferation component of an immune-mediated disorder~~, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent, ~~provided that said composition does not include auranofin and betamethazone dipropionate.~~

Claim 38 has been added as follows:

38. (New) A method of treating an immune-mediated disorder comprising administering a to a patient in need of such treatment a pharmaceutical composition according to claim 29.

### APPENDIX A

1. (Amended) A method of selecting a treatment for an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising identifying the presence of one or both of said components; and selecting at least one corticosteroid which interacts with a gold compound to exhibit preferential synergistic action towards the one components of said disorder if only one component is present or to exhibit equal action towards each component of said disorder if both components are present.
2. (Amended) A method according to claim 1, wherein the disorder has an inflammatory component and a cellular hyperproliferation component.
3. (Amended) A method according to claim 1, wherein the gold compound and the at least one corticosteroid are administered simultaneously.
4. (Amended) A method according to claim 1, wherein the gold compound and the at least one corticosteroid are administered sequentially.
5. (Amended) A method according to claim 4, wherein the at least one corticosteroid is administered after the gold compound.
6. (Amended) A method according to claim 1, comprising selecting at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.
7. A method according to claim 1, wherein the disorder is an immune-mediated dermatological disorder.
8. A method according to claim 7, wherein the disorder is psoriasis.

9. A method according to claim 7, wherein the disorder is dermatitis.
10. A method according to claim 1, wherein the disorder is rheumatoid arthritis.
11. A method according to claim 1, wherein the gold compound is lipid soluble.
12. A method according to claim 1, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards cellular hyperproliferation in preference to inflammation.
13. A method according to claim 12, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and hydrocortisone.
14. A method according to claim 1, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards inflammation in preference to cellular hyperproliferation.
15. A method according to claim 14, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and mometasone furoate.
16. A method according to claim 10, wherein the corticosteroid is selected from the group consisting of hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-privalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

17. A method according to claim 16, wherein the corticosteroid is selected from the group consisting of hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

18. A method according to claim 1, wherein the gold compound is auranofin.

19. A method according to claim 1, wherein the gold compound is administered systemically.

20. A method according to claim 1, wherein the gold compound is administered orally.

21. A method according to claim 1, wherein the gold compound is administered locally.

22. A method according to claim 1, wherein the gold compound is administered topically.

23. A method according to claim 1, wherein the gold compound is administered by intra-articular injection.

24. A method according to claim 1, wherein the at least one corticosteroid is administered systemically.

25. A method according to claim 1, wherein the at least one corticosteroid is administered orally.

26. A method according to claim 1, wherein the at least one corticosteroid is administered locally.

27. A method according to claim 1, wherein the at least one corticosteroid is administered topically.

28. A method according to claim 1, wherein the at least one corticosteroid is administered by intra-articular injection.

29. (Amended) A pharmaceutical composition selected according to the method of claim 1, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

30. A pharmaceutical composition according to claim 29, wherein the composition is formulated for systemic administration.

31. A pharmaceutical composition according to claim 29, wherein the composition is formulated for oral administration.

32. A pharmaceutical composition according to claim 29, wherein the composition is formulated for local administration.

33. A pharmaceutical composition according to claim 29, wherein the composition is formulated for topical administration.

34. A pharmaceutical composition according to claim 29, wherein the composition is formulated for administration by intra-articular injection.

35. A pharmaceutical composition according to claim 29, wherein the corticosteroid is selected from the group consisting of hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-privalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

36. A pharmaceutical composition according to claim 35 wherein the corticosteroid is selected from the group consisting of hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

37. A pharmaceutical composition according to claim 29, wherein the gold compound is auranofin.

38. A method of treating an immune-mediated disorder comprising administering to a patient in need of such treatment a pharmaceutical composition according to claim 29.